REMARKS

Claims 21-55 are pending and under consideration. After entry of this amendment, pending claims will be 21-59. The Examiner is kindly thanked for courtesies extended during telephonic communications, April 18, 2003, and September 5, 2003.

The remarks presented herein are in response to the Office Action mailed November 5, 2002. Applicants timely filed a Notice of Appeal, May 5, 2003, and submit herewith a petition for extension of time that extends the time for response by two months from July 5, 2003 to and including September 5, 2003.

Attached hereto are a Declaration under 37 C.F.R. § 1.131 and a Declaration under 37 C.F.R. § 1.132. Since the rejections in the Office Action mailed November 5 2003 are made over claims amended in a response filed August 14, 2002, the Declarations under 37 C.F.R. §§ 1.131, and 1.132 could not have been submitted in response to an earlier office action.

Amendments to the Specification

Applicants have amended the specification to insert the claim of priority to U.S. provisional application 60/193,181, filed March 30, 2000. Since the claim for priority was made at the time of filing the instant application, and is recorded on the Filing Receipt mailed June 1, 2001, no new matter has been added by way of this Amendment and entry thereof is respectfully requested.

Applicants have also amended the specification to correct several typographical errors, specifically the spelling of "one", "patients", and "interval" on page 15, and the spelling of "ratios" on page 22. These amendments are merely ministerial and do not introduce new matter. Accordingly their entry is also respectfully requested.

New Claims

Applicants respectfully request consideration of new claims 56-59, each of which recites a limitation that the duration of administration is from 2 to 6 weeks. Such claims find support in the specification as filed at page 7, lines 11-13 and 30-32. Accordingly, no new matter is being introduced in claims 56-59. Additionally, Applicants respectfully submit that the limitation of claims 56-59 pertains to a duration of treatment, which corresponds to subject matter already searched by the Examiner. Accordingly, Applicants believe that claims 56-59 do not present any new issues for examination, and entry thereof is respectfully requested.

Declaration Under 37 C.F.R. § 1.132

Applicants bring to the Examiner's attention a Declaration under Rule 132 of the Rules of Practice (the "Retzios Declaration"), executed by Anastassios D. Retzios, a co-inventor of the above-identified patent application. The Retzios Declaration describes a clinical trial and attests to the results obtained in it.

The clinical trial compared oral and intra-nasally administered forms of metoclopramide for treatment of gastroparesis. The trial was a multicenter, controlled, randomized, open-label, parallel design study in patients with diabetic gastroparesis that met certain inclusion and exclusion criteria. (Specification as filed, pages 12–22.) Applicants have discovered that intranasal administration of 10 mg and 20 mg doses of metoclopramide provides greater reduction in the symptoms of gastroparesis when compared to 10 mg oral doses of metoclopramide. (Specification as filed, Tables 1–4.) As discussed in the Retzios Declaration, one of ordinary skill in the art would have expected adverse nasopharyngeal events severe enough to cause a significant fraction of the patient pool to withdraw from the study but, surprisingly, this did not occur.

Claim Rejections Under 35 U.S.C. § 103(a) should be withdrawn

Claims 21–55 are rejected under 35 U.S.C. § 103(a) as being obvious over one or more cited references. As discussed hereinbelow, none of the cited references, or combination of references, renders these claims obvious, and the rejection should be withdrawn.

At the outset, Applicants point out that the U.S. Patent and Trademark Office ("PTO") bears the burden of establishing a *prima facie* case of obviousness. *In re Bell*, 26 USPQ2d 1529 (Fed. Cir. 1993). To establish a *prima facie* case, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify or combine the reference teachings in the manner suggested by the PTO. *In re Rouffet*, 149 F.3d 1350, 47 USPQ2d 1453 (Fed. Cir. 1998). Second, the skilled artisan, in light of the teachings of the prior art, must have a reasonable expectation that the modification or combination suggested by the PTO would be successful. *In re Merck & Co., Inc.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Finally, the prior art reference, or references when combined, must teach or suggest each and every limitation of the claimed invention. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). The teaching or suggestion to make the claimed invention and the

reasonable expectation of success must both be found in the prior art, not in the Applicant's disclosure. *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991). If any one of these criteria is not met, *prima facie* obviousness is not established.

Moreover, Applicants take this opportunity to clarify that the reference Marketing Authorization for Pramidin (hereinafter "Pramidin Marketing Authorization", presented as IDS Ref. AD) is a separate and distinct reference from the "package inserts for Pramidin 10 and Pramidin 20" (hereinafter "the Pramidin Package Inserts") which were presented as IDS Ref. AE. It appears that both the "Pramidin Marketing Authorization" and the "Pramidin Package Inserts" have been collectively referred to as "Pramidin" as part of the rejection of claims 21-55. However, Pramidin Marketing Authorization is to be found in the Official Gazette of the Italian Government ("Gazzetta Ufficiale Della Repubblica Italiana") which was published in December 1997, whereas the Pramidin Package Inserts were supplied with the commercially available product and were not available to the public until April 1999, less than 1 year prior to the filing date of the provisional application from which the instant application claims priority.

In this regard, Applicants bring to the PTO's attention a Declaration under 37 C.F.R. § 1.131 of Laura S. Lehman, David Tierney, Anastassios D. Retzios, Michael Petrone, David Young, Carol B. Trapnell, and Ruth Oliver (the "Rule 131 Declaration"), executed by all of the inventors of the above-identified patent application. The Rule 131 Declaration demonstrates conception of the invention recited in the claims of the above-identified patent application prior to April 1999, coupled with diligence from prior to April 1999 up to actual reduction to practice of the claimed invention and/or until after filing of the provisional U.S. patent application serial no. 60/193,181, filed March 30, 2000, to which the above-identified patent application claims priority. Accordingly, Applicants respectfully submit that the Pramidin Package Inserts are therefore not available as a reference that can be cited against the claims of the above-identified patent application. In view of this, in the arguments presented hereinbelow, when discussing the "Pramidin" portion of the rejection, Applicants will be addressing the Pramidin Marketing Authorization only.

Rejection of claims 30-35, 39-46 and 49-51

Claims 30-35, 39-46 and 49-51 stand rejected under 35 U.S.C. § 103(a) as allegedly being obvious in view of Pramidin. As discussed hereinabove, the PTO has collectively referred to two distinct references as "Pramidin"; therefore this rejection can be more specifically summarized as an allegation that the subject matter recited by these claims is

unpatentable over "Pramidin Marketing Authorization" and "Pramidin Package Inserts". As pointed out hereinabove, however, Pramidin Package Inserts does not constitute a reference that can be cited against the pending claims. Accordingly, Applicants respectfully traverse this portion of the rejection, and address Pramidin Marketing Authorization hereinbelow.

Pramidin Marketing Authorization discloses two compositions for treating gastroparesis of various origin, *i.e.*, Pramidin 10 and Pramidin 20, having 200 mg/ml and 400 mg/ml metoclopramide free base respectively, in addition to other ingredients such as purified water and sorbitol. However, Pramidin Marketing Authorization is silent with respect to both dosage and duration of intranasal administration of metoclopramide for treatment of gastroparesis.

Although the PTO acknowledges that Pramidin is silent with respect to duration of treatment, the PTO has asserted that Pramidin discloses a dosage for treatment such as 20 mg in each nostril 3 times a day. Applicants respectfully point out that Pramidin Marketing Authorization does not, in fact, teach any intranasal dosage let alone an effective one for treatment of gastroparesis.

Accordingly, Applicants respectfully submit that the cited reference (Pramidin) does not teach or suggest each and every element of Claims 30-35, 39-46 and 49-51. Specifically, Pramidin Marketing Authorization fails to teach or suggest a daily dose or a duration of treatment. Therefore, claims 30-35, 39-46 and 49-51 are not obvious in view of Pramidin.

> It is noted that the PTO has suggested that even though the reference
>
> does not specifically disclose a daily dosage for treating gastroparesis, the disclosed daily dosage recommendations are within the required range and it would have been obvious ... to have implemented slight modifications to the teachings in order to have obtained a method of treatment for a specific disorder with a known product at suggested dosage ranges.

The PTO has also suggested that "optimization of concentration ranges will not support the patentability of subject matter." The PTO is reminded that Pramidin Package Inserts, which present dosages, is not available as a reference. Applicants respectfully submit that, since Pramidin Marketing Authorization teaches neither a daily dose, nor a concentration range, nor a duration of administration, identifying a treatment protocol to implement cannot possibly constitute a mere "optimization of concentration ranges." This view is supported by the Retzios Declaration, at paragraph 11.

Accordingly, because Pramidin Marketing Authorization provides no suggestion of Applicants' claimed invention, Applicants respectfully request that the rejection of record be removed.

Rejection of claims 21-29, 36-38 and 47-55

Claims 21-29, 36-38 and 47-55 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Pramidin, in view of product information on Reglan® (hereinafter Robins). As discussed hereinabove, the PTO appears to have combined the separate teachings of the two references Pramidin Marketing Authorization (IDS Ref. AD), and Pramidin Package Inserts (IDS Ref. AE) into a single reference. However, as evidenced by Applicants' Rule 131 Declaration, Pramidin Package Inserts is not available as a reference against the pending claims. Accordingly, Applicants respectfully traverse the remainder rejection.

In rejecting claims 21-29, 36-38 and 47-55, the PTO acknowledges that Pramidin (*i.e.*, Pramidin Marketing Authorization and Pramidin Package Inserts) is silent with respect to duration of treatment. However, the PTO contends that Pramidin discloses a dosage for treatment such as 20 mg in each nostril 3 times a day. As discussed hereinabove, Applicants respectfully point out that Pramidin Package Inserts is not available as a reference, and no dosages can be found in Pramidin Marketing Authorization. Accordingly, since Pramidin Marketing Authorization neither teaches an intranasal dosage for treatment of gastroparesis nor a duration of treatment, such teachings must be found elsewhere in order to sustain the rejection.

Applicants respectfully submit that the teachings missing from Pramidin Marketing Authorization are not supplied by Robins. The PTO has indicated that Robins teaches administering metoclopramide orally for relief of symptoms associated with diabetic gastroparesis, in doses of 10 mg, 3 times a day, for two to eight weeks. As acknowledged by the PTO, the dosages in Robins are lower than those recited in Applicants' pending claims. Additionally, in respect of claims 28 and 29, which recite daily dosages in the range 0.1 to 2.5 mg/kg, the PTO has pointed out that Robins indicates "[l]ower doses (2.5-5mg) or 0.1 mg/kg are recommended for pediatric patients and elderly ... (see page 12)." However, Applicants respectfully submit that this is a misreading of Robins. The stated doses (on page 12 of Robins) are to "facilitate small bowel intubation" and not for the treatment of gastroparesis.

In respect of the dosages recited in claims 22-27, 36-38 and 47-55, neither Robins nor Pramidin Marketing Authorization indicates that such dosages are efficacious in humans, via any method of administration, for a duration of two to eight weeks.

In respect of duration of treatment, however, the mere fact that Robins teaches *oral* administration of metoclopramide for two to eight weeks does not suggest that *intranasal* administration over the same period would be viable. In particular, Applicants draw the PTO's attention to the Retzios Declaration, at paragraph 12, wherein Anastassios D. Retzios states that "one familiar with the field ... would not have predicted that the same protocol would be effective for both an oral and an intranasal administration." Applicants respectfully note, once again, that Pramidin Marketing Authorization is also silent in respect of duration of treatment for intra-nasal administration of metoclopramide.

Accordingly, Applicants respectfully submit that Pramidin Marketing Authorization and Robins, in combination, do not provide a teaching or suggestion of Applicants' claimed invention.

Furthermore, Applicants also assert that one of ordinary skill in the art would not have been motivated to combine the teachings of Pramidin Marketing Authorization and Robins because Robins indicates that adverse CNS effects can result from administration of metoclopramide. As discussed in the Retzios Declaration, at paragraph 14, "it would have been reasonably expected that metoclopramide administered intranasally in doses of 10 mg and 20 mg q.i.d., (*i.e.*, in doses of 40–80 mg per day) for periods up to 8 weeks, would give rise to adverse CNS effects in a significant proportion of a patient pool." Thus, in respect of the dosages recited in claims 22-27, 36-38 and 47-55, given the known adverse CNS effects associated with oral administration of Reglan®, one would not have been motivated to increase the dosages in an intranasal administration in order to arrive at Applicants' claimed invention.

Finally, even assuming, *arguendo*, that a suggestion of the claimed invention did exist (which it does not), Applicants point out that one of ordinary skill in the art would have had no reasonable expectation, in combining the teachings of Robins with those of Pramidin Marketing Authorization, that the claimed invention could successfully be practiced. In fact, in complete contrast, one of ordinary skill in the art would have expected adverse nasopharyngeal events to develop that would preclude a significant portion of the patient pool from tolerating intranasally administered metoclopramide in the durations and dosages claimed by Applicants. As pointed out by Dr. Retzios in the attached Retzios Declaration at paragraphs 16, 24 and 33, severe adverse naso-pharyngeal effects were expected in at least a significant proportion of patients subjected to intranasal administration of metoclopramide for the duration recited in claims 21-29, 36-38 and 47-55. Such adverse nasopharyngeal effects would have undermined the efficacy of metoclopramide administered intranasally.

Although it was expected that patients being administered intranasal metoclopramide would experience increased incidence of adverse nasopharyngeal effects, it was unexpected that no patients would discontinue treatment because of adverse nasopharyngeal effects. (Retzios Declaration, paragraph 33.) That is, it was expected that at least a certain number of patients receiving intranasal metoclopramide would experience adverse nasopharyngeal effects severe enough to precipitate withdrawal from the study. Surprisingly, this was not the case.

Accordingly, one of ordinary skill in the art would not have predicted that metoclopramide could be used successfully intranasally for the recited durations, and therefore it would not have been obvious to have combined the teachings of Pramidin Marketing Authorization and Robins. Thus, Applicants respectfully request that the rejection of record be removed.

Rejection of claims 21-55

Claims 21-55 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Robins in view of U.S. Patent No. 4,624,965 to Wenig (hereinafter "Wenig"). Applicants respectfully traverse the rejection. First, one of ordinary skill in the art would not have been motivated to combine the teachings of Robins and Wenig; second, Robins and Wenig, in combination, do not teach or suggest Applicants' invention; and finally, one of ordinary skill in the art would not have had a reasonable expectation of success in utilizing the combined teachings for the treatment of gastroparesis.

Applicants respectfully assert that one of ordinary skill in the art would not have been motivated to combine the teachings of Robins and Wenig. This is for two reasons. First, Wenig is silent as to the merits of metoclopramide for the specific treatment of symptoms of gastroparesis; instead Wenig addresses anti-nausea, and anti-emetic indications only. Furthermore, the only application of metoclopramide to humans, taught by Wenig in Examples 8 and 9, are not for treating gastroparesis. Example 8 of Wenig compares blood levels in humans achieved with various doses of oral, intramuscular, and nasal formulations of metoclopramide, for an unspecified period of time, without specifying an indication. Example 9 of Wenig describes application of 40 mg doses of metoclopramide intranasally to a patient, but one who is suffering not from gastroparesis, but from a mechanical bowel obstruction. Thus, Wenig does not show or suggest that nasally administered metoclopramide is appropriate for gastroparesis.

Second, one of ordinary skill in the art in possession of the teachings of Robins would conclude that acceptable formulations for treating gastroparesis already exist, namely oral and injectable forms. Such a person of ordinary skill reading Robins would thus not have been motivated to consider an alternative formulation such as an intranasal formulation. Furthermore, as can also be seen from the Retzios Declaration, nothing was known of the effect on patients of intranasally administered metoclopramide at either the durations or dosages recited in Applicants' claims. (Retzios Declaration, paragraphs 15 and 23). Accordingly, one of skill in the art would not have been motivated to combine the teachings of Robins and Wenig in order to arrive at Applicants' claimed invention.

Additionally, Applicants respectfully submit that, contrary to the PTO's views, even if a motivation to combine were to be assumed, Wenig does not supply a sufficient teaching of dosages that, in combination with Robins, would either teach or suggest Applicants' claimed invention to one of ordinary skill in the art. The PTO states that Robins teaches oral or injectable forms of metoclopramide for treatment of gastroparesis, and that the duration of treatment is from 2 to 8 weeks. However, as discussed hereinabove, Robins does not teach Applicants' claimed dosages, and does not teach intranasal formulations of metoclopramide. Wenig does not provide the dosages that are missing from Robins.

In respect of claims 30-35, Wenig does not teach dosing for administering either nasal spray or drop formulations for treatment of the symptoms of gastroparesis in humans. In particular, Examples 2–5 of Wenig teach application of metoclopramide (MCP) or metoclopramide hydrochloride (MCP.HCl) in nasal drops to animals, but not to humans; Example 7 demonstrates toxicity studies of a gel formulation of MCP on rabbits; and Example 8 of Wenig compares blood levels in humans achieved with various doses of oral, intramuscular, and nasal formulations of metoclopramide, for an unspecified period of time, but say nothing about the treatment of the symptoms of gastroparesis; Example 9 of Wenig describes intranasal application of metoclopramide to a patient suffering from a mechanical bowel obstruction, but not gastroparesis. Accordingly, not even Examples 8 or 9 of Wenig offer one of ordinary skill in the art any indication that intranasal application of metoclopramide at the reported dosage could be successful for treating gastroparesis. Therefore, Wenig does not suggest to one of ordinary skill in the art that there are dosages applicable for treating gastroparesis by intranasal administration, or what such dosages could be.

In respect of claims 21-29, 36-38, and 39-55, Wenig does not provide one of ordinary skill in the art with sufficient guidance to devise a duration of treatment for relieving the

symptoms of gastroparesis. For example, neither of Examples 8 or 9 of Wenig that discuss intranasal administration of metoclopramide in humans indicates a duration of administration. Thus, Wenig provides no teaching of the duration of safe application of metoclopramide intranasally. As discussed hereinabove, in the Retzios Declaration, at paragraph 12, one of ordinary skill in the art would not ordinarily predict that the same protocol would be effective for both orally and intranasally administered forms of the same drug.

Accordingly, the combination of Wenig and Robins does not render Applicants' claims obvious at least because one of ordinary skill in the art is not provided with a teaching or suggestion that intranasal metoclopramide could be used to treat gastroparesis in humans at Applicants' recited doses and for Applicants' duration of treatment. Accordingly, Applicants respectfully request that the PTO remove the rejection of record.

Finally, as discussed hereinabove, because of the lack of knowledge of the behavior of metoclopramide when administered intranasally for the duration of time, and at the doses reported and claimed by Applicants (Retzios Declaration, at paragraphs 15 and 23), one of ordinary skill in the art would not have had a reasonable expectation of success in treating gastroparesis according to Applicants' claimed invention. Certainly, it would have been surprising to one familiar with the field that intranasally administered metoclopramide was able to treat gastroparesis at least as effectively as orally-administered metoclopramide. (Retzios Declaration, at paragraph 10).

Additionally, one of ordinary skill in the art would not have had a reasonable expectation of success in combining the teachings of Wenig and Robins, in order to arrive at Applicants' claimed invention. First, because of the adverse CNS effects reported by Robins, as discussed hereinabove. One of ordinary skill in the art would not have expected that administering metoclopramide to patients at Applicants' claimed dosages and durations of treatment would succeed safely. Second, as presented in the Retzios Declaration at paragraphs 16, 24 and 33, one of ordinary skill in the art would have expected a greater instance of adverse nasopharyngeal reactions upon administering metoclopramide for the duration of treatment recited in Applicants' pending claims than in fact was found.

Accordingly, and in summary, not only was efficacy as a method of treating gastroparesis not disclosed in Wenig, but no indication of the effective duration of treatment for intranasal administration of metoclopramide was taught. Thus, one of ordinary skill in the art would not have considered combining the teachings of Wenig and Robins to administer metoclopramide intranasally to treat gastroparesis. Thus, Applicants respectfully request that the rejections under 35 U.S.C. § 103(a) be removed.

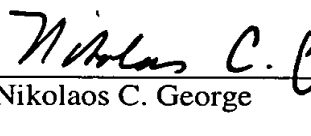
CONCLUSION

Applicants submit that Claims 21-59 satisfy all of the criteria for patentability and are in condition for allowance. An early indication of the same is therefore kindly solicited.

No fees in addition to the extension fee are believed due in connection with this response. However, the Commissioner is authorized to charge all required fees, or credit any overpayment, to Pennie & Edmonds U.S. Deposit Account No. 16-1150 (ref. 7960-131).

Respectfully submitted,

Date: September 5, 2003



39,201

Nikolaos C. George (Reg. No.)

For Brian M. Poissant (Reg. No. 28,462)
PENNIE & EDMONDS LLP
1155 Avenue of the Americas
New York, New York 10036-2711
(212) 790-9090